# Lactate: Where Are We Now?

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**KEYWORDS**

• Sepsis • Shock • Tissue perfusion • Early goal directed therapy • Hemodynamics

**KEY POINTS**

- Lactate is a rapidly available variable that is closely linked to morbidity and mortality in almost every critically ill patient.
- A decrease in lactate levels during initial resuscitation of a patient with circulatory dysfunction is a universally good sign.
- Lactate clearance is a function of production and uptake of lactate, mostly by liver and kidney, followed by metabolism that results in a given serum lactate concentration. Lactate clearance in clinical practice refers to the changes in lactate over time.
- Using lactate levels as a marker of tissue hypoperfusion has limitations, especially in septic shock patients, and is likely to be limited to the initial hours of resuscitation.
- When initial therapy in the first 6 to 8 hours of septic shock resuscitation is aimed to decrease lactate levels guided by parameters of tissue perfusion this is likely to improve outcome of the patient.

## INTRODUCTION

Following the definition of a biomarker lactate seems to be the ideal one in critically ill patients. Increased lactate levels are a universal sign of an abnormal condition. When using the correct treatment to correct the causing mechanism, lactate levels change quickly. A decrease in lactate levels following institution of treatment thus gives the clinician guidance on its adequacy and may serve to adjust treatment when needed. However, in contrast to what some guidelines suggest, lactate is not an easy to use parameter and an advice to measure it without a clinical direction on how to respond is not the way to go. Opinions on the clinical value of lactate levels still spur a lot of discussion[1–3] related to the many pitfalls of using lactate in critically ill.[4]

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In clinical conditions we characterize circulatory dysfunction by a combination of abnormalities in different systems. Without a particular order of importance, it may consist of abnormal hemodynamic parameters like blood pressure and heart rate, abnormal tissue perfusion parameters like a cold, discolored sweaty skin, altered mental state and decreased urine production and abnormal metabolic parameters like lactate, arterial pH, and base excess. Under normal conditions, oxygen demand dictates oxygen delivery and is thus equal to oxygen consumption. Therefore, a decrease in oxygen consumption during unchanged oxygen demand denotes a state in which the delivery of oxygen to the tissues is inadequate to meet the demands for normal tissue function (tissue hypoxia) that will result in tissue damage and organ dysfunction. Invariably in both experimental and clinical conditions this situation is characterized by a sharp rise in lactate levels.[5,6] As increased lactate levels in critically ill patients have also been associated with this phenomenon[7,8] and increased lactate levels are related to the presence and severity of organ dysfunction,[9,10] increased lactate levels have been seen as a hallmark of circulatory dysfunction and tissue damage.

In this article, we review the current states on how to appropriately use lactate levels to that end and how they can be used to diagnose and treat circulatory dysfunction.

## METABOLISM OF LACTATE

Under normal conditions, the metabolism of lactate produces a small amount of ATP in the presence or absence of a functional Krebs cycle. However, by accelerating the process of glucose metabolism, much more ATP can be generated.[11] Therefore, a clinical context associated with increased glucose metabolism might lead to increased lactate levels as the capacity of the Krebs cycle is limited. Many situations and treatments in critically ill patients lead to increased glucose metabolism. Increased sympathetic nervous system activation, prominently present in shock states, is only one of them.[12] In these conditions, lactate might even serve as a fuel being exchanged between tissues (liver, kidneys, muscles) and even cells (astrocytes, neurons) through lactate shuttles.[13,14] In contrast with the Cori cycle (hepatic and renal gluconeogenesis) requiring oxygen, the interorgan/cellular exchange does not make this an interesting energy transport mechanism.[15] Even exogenous lactate can be used as a fuel in this context.[13] Therefore, the old concept of lactate being an indicator of the presence of tissue hypoxia in shock states has been challenged and especially in sepsis, where lactate clearance is impaired, this relationship might be more problematic than suggested in guidelines[4,16]

## LACTATE AND TISSUE HYPOPERFUSION

Oxygen delivery is a function of hemoglobin levels, arterial oxygen saturation, and cardiac output (and its distribution). In experimental conditions, decreasing any of these components of oxygen delivery will result in a decrease in oxygen consumption when a critical level is reached.[6,17] This state of oxygen delivery–dependent oxygen consumption is a hallmark of tissue hypoxia and further reductions in oxygen delivery will immediately result in sharp decreases in oxygen consumption (below the baseline level reflecting the demand for oxygen) and increases in lactate levels. Also, in clinical conditions, this supply dependent state is characterized by increased lactate levels.[7] The study by Ronco and colleagues[5] showed that this phenomenon also occurs when therapy is withdrawn during end-of-life care. In experimental conditions, reversing this state of supply dependency, corrects lactate levels to normal baseline levels.[18] Clinically, Friedman and colleagues[8] showed that supply dependency is present in the early phase of septic shock, whereas in the post resuscitation phase supply dependency was absent and lactate levels were normal. In addition, observational studies

have associated increased morbidity and mortality to the presence of other markers of tissue hypoperfusion in patients with sepsis.

In the presence of normal oxygen delivery values, abnormal microcirculatory perfusion may still be present[19] and thus there will be limited cellular oxygen availability. Particularly in sepsis, microcirculatory derangement may lead to insufficient oxygen that is delivered to the cell, thereby increasing lactate levels.[17] This is indirectly illustrated by the observation that increased lactate levels have been associated with abnormal microcirculatory perfusion[20] and that improving capillary perfusion has been associated with a reduction in lactate levels in patients with septic shock, independent of changes in systemic hemodynamic variables.[21] In addition, normalization of tissue perfusion parameters has been associated with a sharp decrease in lactate levels.[22]

Nevertheless, given the abnormal metabolism in sepsis[23–25] and the decreased clearance of lactate[26–28] even restoration of microcirculatory perfusion in these conditions may still be associated with increased lactate levels.[29] This in contrast with low cardiac output forms of circulatory failure where correction of microcirculatory perfusion is associated with normalization of lactate levels.[29] Therefore, especially in septic shock conditions, the exclusive use of increased lactate levels to determine the presence of tissue hypoxia, following the initial period of resuscitation, is limited.[30] Additional parameters reflecting tissue perfusion and metabolism have been proposed to aid in the diagnosis.[22,31–33] Also, the lactate to pyruvate ratio has been proposed to aid in the diagnosis of hypoxia related tissue metabolism.[34–36] Although clinically available as a micro dialysate technique in brain tissue monitoring,[37] the interpretation in relation to tissue hypoxia is not straight forward but rather a complex parameter of metabolism.[38,39]

## CLEARANCE OF LACTATE

As the blood lactate level is a result of the production and clearance, an impairment in the latter may thus result in increased lactate levels. Several conditions have been associated with impaired clearance. Liver dysfunction/failure, cardiac surgery, and sepsis have all been associated with decreased clearance capacity.[24,26,40,41] In clinical practice, lactate clearance has been used to describe the change in lactate levels over time. Although technically not correct,[4,42] the use of lactate clearance has been stimulated by studies linking the relative decrease of lactate levels over time to the patient's response to therapy and ultimately outcome.[43–48] In summary, almost in any context of critical illness, decreases in lactate levels following start of treatment are associated with improved outcome.[49] Meta-analysis of studies using decreases in lactate as a clinical endpoint showed improved survival both in hyperlactatemic patients as in patients with severe sepsis and septic shock.[50,51]

## GOAL-DIRECTED THERAPY USING LACTATE LEVELS

Given the strong relationship among increased lactate levels tissue perfusion, organ failure, and ultimate outcome, this biomarker is frequently used in clinical practice to guide therapy. However, only a limited number of randomized studies have evaluated the value of this strategy.

Many studies evaluating the use of early goal-directed therapy (EGDT) aiming to optimize blood pressure, preload status, and tissue perfusion in patients with sepsis have shown minimal results in contrast to the first landmark study by Rivers and colleagues[52] using this concept. Three large randomized studies[53–55] randomizing more than 4000 patients in total did, not show a survival benefit when using the broad elements of EGDT. Although there might have been a survival benefit in patients with a high initial lactate level (>5.0 mmol/L),[53] lactate levels were not used to adjust therapy

by protocol in these studies. Important to recognize here is that the landmark study by Rivers and colleagues[52] was started in native sepsis patients without any previous treatment, whereas the recent EGDT studies have all been done in patients who had already received some early treatment, in most cases fluid resuscitation or even already start of vasopressor therapy.[56]

In a study in patients with early sepsis by Jones and colleagues,[57] therapy aimed to normalize central venous oxygenation ($ScvO_2$) was compared with therapy aimed to decrease lactate levels by at least 10% in the 6-hour duration study protocol. In this study, fluid resuscitation in both groups was aimed to increase central venous pressure to 8 mm Hg or higher, vasopressors were used to maintain a mean arterial pressure (MAP) of 65 mm Hg or higher, and dobutamine and blood transfusions were used where needed to increase $ScvO_2$. In the lactate-guided group, the same interventions were used; however, $ScvO_2$ was not available in these patients and substituted with the lactate target of a 10% decrease in the first 2 hours or longer. The hospital mortality in the 2 groups, of each 150 patients, was lower in the lactate-guided group (17% vs 22%), although this difference was not statistically significant (difference 6; 95% CI −3% to 15%).

In a randomized trial in the Netherlands, Jansen and colleagues[58] studied 348 patients with a lactate level of more than 3.0 mmol/L irrespective of their diagnosis. Following the measurement of central venous oxygen saturation ($ScvO_2$), therapy was directed to optimize oxygen delivery and reduce oxygen demand in the lactate group. The aim of the protocol was to decrease lactate by at least 20% every 2 hours for the duration of the intervention period (first 8 hours of admission). The control group received standard treatment where lactate levels were not available. This combined use of $ScvO_2$ and lactate decreases resulted in an improvement in hospital survival when corrected for baseline imbalances (hazard ratio 0.61 [CI: 0.43–0.87]). When combining the patients with sepsis from this study with the study by Jones and colleagues[57] and two Chinese studies, using lactate to guide therapy in sepsis patients was shown to improve outcome.[50]

In a recent study in 424 patients with septic shock, Hernandez and colleagues[56] compared a strategy to decrease lactate levels similar to the study by Jansen and colleagues[58] with a strategy to normalize peripheral capillary refill time (CRT). In both groups, the protocol to reach the therapeutic goal was similar, with only a difference in the ultimate therapeutic goal: CRT of 3 seconds or less or a decrease in lactate by 20% every 2 hours for the duration of the 8-hour intervention period. In this study, there was improved survival in the group using CRT as the endpoint of resuscitation, although this was not statistically significant (34.9% vs 43.4% 28-day mortality, $P = .06$). However, the patients in the CRT-guided resuscitation had significantly less positive fluid balances during the intervention period and a faster recovery of organ failure when compared with the lactate-guided resuscitation.

## HOW TO USE LACTATE IN CLINICAL PRACTICE

An increased lactate should always be a warning signal to the treatment team requiring immediate attention. The first line of assessment is very straightforward: the higher the lactate level, the higher the urgency. In the control group of the recent study by Jansen and colleagues,[58] in which patients with a suspected source of increased lactate levels other than circulatory were excluded, survival rapidly decreased with increasing initial lactate levels (**Fig. 1**). These data are compliant with older data in which increasing lactate levels were associated with rapidly decreasing survival.[59,60]

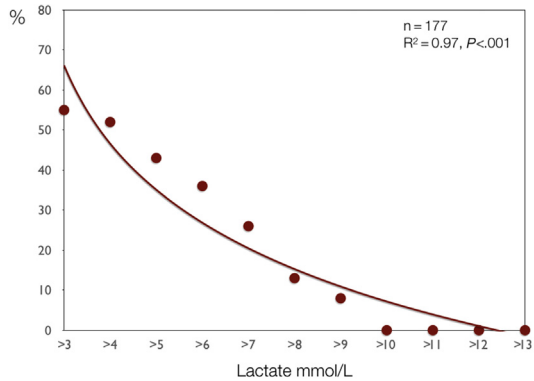


**Fig. 1.** Relationship between initial lactate level and survival in patients admitted with a lactate level of 3 mmol/L or more. Patients consist of the control group in the study by Jansen and colleagues.[58] (*From* Jansen TC, van Bommel J, Schoonderbeek FJ, et al. Early Lactate-Guided Therapy in Intensive Care Unit Patients A Multicenter, Open-Label, Randomized Controlled Trial. Am J Respir Crit Care Med 2010;182(6):752-761.)

The first line of action should then be to create context (Fig. 2). If the increased lactate is unlikely to be associated with decreased tissue perfusion but rather metabolic derangements or other causes,[12] this should be investigated and appropriate measures should be taken. In general, the urgency and line of actions in these contexts may be very different where generalized seizures, thiamine deficiency, and carbon monoxide or cyanide intoxication are extreme examples.[61–64]

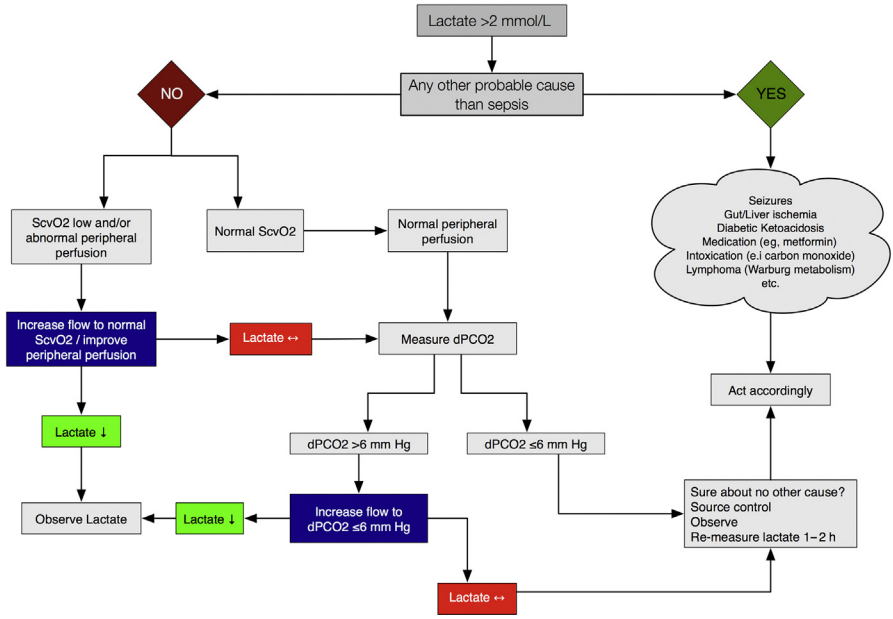


**Fig. 2.** Steps to guide treatment using repeated measurements of lactate using central venous oxygen saturation ($ScvO_2$) and central venous-to-arterial $P_{CO_2}$ difference (dPCO2). (*From* Hernandez G, Bellomo R, Bakker J. The ten pitfalls of lactate clearance in sepsis. Intensive Care Med 2018;45(1):82-85; with permission.)

When there are signs of impaired tissue perfusion (eg, hypotension, tachycardia, abnormal peripheral perfusion, altered mentation), a measurement of $ScvO_2$ should be done. When normal, adding measurements of the delta-$PCO_2$ (difference between central venous and arterial $P_{CO_2}$)[22] or a surrogate of the respiratory quotient (venous-arterial CO2 to arterial-venous O2 content difference ratio)[32] or the venous-arterial CO2 to arterial-venous O2 difference ratio[65] could help to diagnose tissue hypoperfusion that would require hemodynamic and microcirculatory perfusion improvements. Treatment should result in a rapid decrease or normalization of lactate levels and the parameters of tissue hypoperfusion.[30,43,66] Current evidence suggests to repeat measurements every 1 to 2 hours.[49] Given the available studies, targeting increased lactate levels by general optimization of perfusion to improve outcome is limited to the initial hours of admission. In the studies presented, this would be the first 6 to 8 hours of admission. Some guidelines suggest that the patient should be resuscitated to normalize lactate levels. Although this may be appropriate in the large community of patients, it does not fit an individualized approach where up to 50% of surviving patients with sepsis may still have increased lactate levels 24 hours after intensive care unit admission.[30] However, persistently increased lactate levels should urge the clinician to review diagnosis and adequacy of the treatment of the cause of increased lactate levels.

## SUMMARY

When used correctly, lactate levels may aid in diagnosing and treating patients. Changes in lactate can provide an early and objective evaluation of the patient's response to therapy. Given current evidence, increased lactate levels in the presence of other markers of tissue hypoperfusion should require immediate hemodynamic optimization directed to improving tissue perfusion. Lactate levels in the absence of other marker of tissue hypoperfusion or beyond the first 8 hours of treatment should be used with caution and should warrant reassessment of diagnosis and the adequacy of the additional supporting treatment.

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